14. EVALUATION OF NIPAH VIRUS AS A HUMAN AND ANIMAL BIOLOGICAL TERRORISM AND WARFARE AGENT

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INTRODUCTION

In July 1999, the delegation of the Republic of Croatia to negotiations in Ad Hoc group of States Parties of BTWC proposed including Nipah virus in the list of animal pathogens. This paper describes an evaluation of Nipah virus as a biological agent for terrorism or warfare.

An outbreak of disease caused by Nipah virus occurred during October 1998 and April 1999. At least 258 persons developed Nipah encephalitis and 106 of them have died. The Nipah virus outbreak also devastated Malaysia's pig-farming industry.

The Nipah virus or so-called Hendra-like virus (*Paramyxovirus* strain) appears to have developed from the virus causing Nipah swine encephalitis (zoonotic infection). Virus is named after the village Kampung Baru Sungai Nipah in Negri Sembilian State, in western Malaysia where University Malaya experts first detected it on March 18, 1999. Nipah virus belongs to the *Paramyxovirus* strain, which shows similarities to the Hendra virus, which was discovered in Australia in 1994. Molecular analyses have confirmed that Nipah virus and Hendra virus are closely related, but different viruses. The N, C, P, V, M, F and G genes of Nipah virus have nucleotide sequence homologies ranging from 88% to 70%, and predicted amino acid homologies ranging from 92% to 67%, in comparison with Hendra virus. The intergenic regions and start/stop signals of the two viruses are identical. They are substantially different from, and have larger genomes than, previously known paramyxoviruses.

The name Porcine Respiratory and Encephalitis Syndrome (PRES) is proposed as the technical name because of the pronounced respiratory and neurologic syndromes associated with the pig disease. The unusual loud barking cough, is another characteristic feature of the disease that differs from the other known respiratory diseases of pigs found in Peninsular Malaysia and thus suggests 'Barking Pig Syndrome' as a common name of the disease. Pathogenesis is still undetermined.

The mechanism of transmission of Nipah virus has not been determined, although infection by direct contact is likely. Causes and contributing factors are movement of pigs and direct pig to pig contact either by mouth, by the respiratory route or aerosol from urinary excretions. The virus can be transmitted from pigs to humans via direct contact with sick pigs through the animals' blood, urine, bronchial secretion and amniotic fluid and other body fluids. Human-to-human transmission of the Nipah virus appears to be low, but may be possible. Because of that, people working in the pig industry or the hospital staff providing intensive care to patients must practice "barrier nursing." The incubation period is from 7 to 21 days. Clinical signs include respiratory disorder characterized by dyspnoea, convulsions and death occurring within several hours. In humans symptoms include rapid labored breathing and very harsh explosive cough. In sows disease may be more pronounced with severe breathing difficulties, pneumonia, mucopurulent discharges from the nose convulsions and death.

Generally mortality of infected pigs is low but morbidity is very high. Researchers believe that fruit bats related to the *Pteropus* species (Pteropus hypomelanus or Island Flying

fox and Pteropus vampyrus or Malayan flying fox or Large fruit bat), which carry Hendra virus, are natural hosts of Nipah virus and may be the original "reservoir" of the disease. Nipah encephalitis and Japanese encephalitis have similar symptoms but patients infected with the Nipah virus deteriorated very rapidly. The mortality rate for human disease caused by Nipah virus is 40% but with dual infection - Japanese encephalitis virus and Nipah virus is 52%.

Diagnose is by serological tests, virus isolation and identification. Laboratory tests include serological test using enzyme linked immunosorbent assay (ELISA) for Nipah, is currently available. Laboratory diagnosis using serum neutralization test (SNT); polymerase chain reaction (PCR) and virus isolation is recommended to be carried out in a biosecurity level BL-4 laboratory.

Treatment is not recommended at all since the disease is transmissible to human. So far, treatment using hyperimmune serum has also not been tried in human.

Animal pathogens as a biological terrorism or warfare agents have the capacity to cause disease and potentially be used to threaten animals. From a social-economic and significant adverse human health impacts, animal pathogens must be evaluated and prioritized. This paper is focused on evaluation of Nipah virus as an animal and human terrorism and warfare agent and compared with other pathogens. This evaluation can serve as the basis for scientific discussion and as help on defining the list of biological agents and toxins in relation to BTWC.

MATERIALS AND METHODS

The criteria we used for evaluation of Nipah virus as a human and animal warfare and terrorism agent, we compiled from several sources such as criteria for selection of biological agents used for negotiations in Ad-hoc Group of States Parties of BTWC, the Australia Group, the Centers for Disease Control and Prevention, Food and Agriculture Organization (FAO) and International Office of Epizootics (OIE). Rankings of Nipah virus as a human and animal warfare and terrorism agent are shown in the tables.

CRITERIA FOR HUMAN PATHOGENS AS WARFARE AGENTS

1. Agents known to have been developed, produced, stockpiled or used as weapons (+).
2. Likely methods and high level of dissemination or contamination a large area as a virulent agent in quantities that could effect large populations: by aerosol or spores in aerosol (+++), infected vector (++), and sabotage (food and water supply) (+).
3. Low infection dose and short incubation or latent period (+).
4. High level of morbidity: higher rating (++) if clinical disease requires hospitalization for treatment including supportive care and lower rating (+) if outpatient treatment is possible for most cases.
5. High level of contagiuousness or transmissibility man to man or high level of infectiousness/intoxication by contact (+), by respiratory route (++), or both (+++).
6. High level of mortality: agents with an expected mortality of ≥50% were rated higher (+++), and with lower expected mortalities (21-49%=++, and <21%=+).
7. Stability in the environment (+).
8. No effective prophylaxis (i.e. immune sera, vaccines or antibiotics) and/or therapy commonly available and widely in use (+).
9. Difficulty to diagnose/detect or identify at the early stage (+).
10. Ease of production and transportation (+).

CRITERIA FOR HUMAN PATHOGENS AS A TERRORISM AGENTS

1. Agents known to have been developed, produced, stockpiled or used as weapons (+).
2. Likely methods and high level of dissemination or contamination a large area as a virulent agent in quantities that could effect large populations: by aerosol or spores in aerosol (+++), infected vector (++), and sabotage (food and water supply) (+).
3. Low infection dose (+).
4. High level of morbidity: higher rating (++) if clinical disease requires hospitalization for treatment including supportive care and lower rating (+) if outpatient treatment is possible for most cases.
5. High level of contagiuousness or transmissibility man to man or high level of infectiousness by contact (+), by respiratory route (++), or both (+++).
6. High level of mortality: agents with an expected mortality of ≥50% were rated higher (+++), and with lower expected mortalities (21-49%=++, and <21%=+).
7. Stability in the environment (+).
8. No effective prophylaxis (i.e. Immune sera, vaccines or antibiotics) and/or therapy commonly available and widely in use (+).
9. Short incubation period (+).
10. Difficulty to diagnose/detect or identify at the early stage (+).
11. Ease of production and transportation (+).

CRITERIA FOR ANIMAL PATHOGENS AS BIOLOGICAL WARFARE AGENTS

1. Agents known to have been developed, produced or used as weapons (Weaponized);
2. Agents which have severe socio-economic and/or significant adverse human health impacts;
3. High morbidity and/or mortality rates;
4. Short incubation period;
5. Difficult to diagnose/identify at an early stage;
6. High transmissibility and/or contagiousness;
7. Lack of availability of cost effective protection/treatment;
8. Low infective/toxic dose;
9. Stability in the environment;
10. Ease of production.

CRITERIA FOR ANIMAL PATHOGENS AS BIOLOGICAL TERRORISM AGENTS

1. Agents which have severe socio-economic and/or significant adverse human health impacts (+);
2. High morbidity rate (+).
3. High mortality rates: agents with an expected mortality of ≥50% were rated higher (+++), and with lower expected mortalities (21-49%=++, and <21%=+);
4. Short incubation period and/or difficult to diagnose/identify at an early stage (+);
5. High transmissibility and/or contagiousness high level of infectiousness/ intoxication by contact (+), by respiratory route (++), or both (+++);
6. Lack of availability of cost effective protection / treatment (+);
7. Low infective dose (+);
8. Stability in the environment (+);
9. Ease of production (+).

CONCLUSION

Many animal and human pathogens can be used as terrorism and warfare biological agents and cause illness. Having a defined and good method for evaluating biological threat agents such as animal and human pathogens allows for more objective evaluation newly emerging potential threat agents. This method of evaluation can help focus public health activities, agriculture activities related to bioterrorizm detection and response. Nipah virus was deleted from the list of animal pathogens in the Rolling Text of the future Protocol of BTWC on 19th session of Ad-hoc group of States Parties of BTWC. Since Nipah virus satisfies the principle criteria, it can be recommended for inclusion in the lists of animal and human pathogens as warfare and terrorism agent.

KEYWORDS

Nipah virus, biological terrorism, and biological warfare agent

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Table 1. Human pathogens (viruses) assessment according to criteria for selecting pathogens as biological warfare agents.

Viruses	Weapo -nized	High level of dissemi -nation	Low infec- tion dose	High level of morbi- dity	High con- tagiousness (transmiss- ibility man to man)	Infection by variety of route (respira- tory route)	High level of mortality	Stability in the environ- ment	Difficulty of detection/ identifi- cation	No effective prophylax is and/or therapy	Ease of produ- ction	Totals +/-
1. Ebola virus	+	+	+	+	+	+	+	-	+	+	+	10/1
2. Crimean-Congo HF virus	+	+	+	+	-	+	+	+	+	+	+	10/1
3. Marburg virus	+	+	+	+	+	+	+	-	+	+	+	10/1
4. Variola major virus	+	+	+	+	+	+	+	+	+	-	+	10/1
5. Lassa fever virus	+	+	+	+	-	+	+	+	+	+	+	10/1
6. Machupo virus	-	+	+	+	+	+	+	-	+	+	+	9/2
7. Junin virus	-	+	+	+	-	+	+	+	+	+	+	9/2
8. Monkeypox virus	-	+	+	+	-	+	+	+	+	+	+	9/2
9. EEE virus	+	+	+	+	-	-	+	-	+	+	+	8/3
10. Tick-borne enceph. virus	+	+	+	+	-	-	+	+	+	-	+	8/3
11. VEE virus	+	+	+	+	-	+	+	-	+	-	+	8/3
12. WEE virus	+	+	+	+	-	+	+	-	+	-	+	8/3
13. Yellow fever virus	+	+	+	+	-	+	+	-	+	-	+	8/3
14. Sin Nombre virus	-	+	+	-	-	+	+	+	+	+	+	8/3
15. Hantaan virus	+	+	+	-	-	+	-	+	+	+	-	7/4
16. Rift Valley fever virus	+	+	+	+	-	-	-	+	+	-	+	7/4
17. Nipah virus	-	+	+	-	-	-	+	+	+	+	-	*6/5*
18. Chikun-Gunya fever virus	-	+	+	-	-	+	-	-	+	+	+	6/5
19. Dengua fever virus	+	+	+	+	-	-	-	-	+	+	-	6/5
20. Omsk HF virus	-	+	+	+	-	-	-	-	-	+	+	6/5

Table 2. Human pathogens (viruses) assessment according to criteria for selecting pathogens as biological terrorism agents.

Viruses	Weapo-nized	High level of dissemi-nation	Low infec-tive dose and short incubation period	High level of morbi-dity	High contagiousness/ transmissibility by contact, respiratory route, or both	High level of mortality	Stability in the environ-ment	Difficulty of detection/ identification	No effective prophylaxis and/or therapy	Ease of produ-ction	Total (17)
3. Ebola virus	+	+++	+	++	+	+++	-	+	+	+	14
9. Marburg virus	+	+++	+	++	+	+++	-	+	+	+	14
1. Crimean-Congo HF virus	+	+++	+	++	+	++	+	+	+	+	14
12.Variola major virus	+	+++	+	+	+++	++	+	+	-	+	14
7. Lassa fever virus	+	+++	+	++	+	++	+	+	+	+	14
8. Machupo virus	-	+++	+	++	+	+++	-	+	+	+	13
16.Monkeypox virus	-	+++	+	+	++	++	+	+	+	+	13
10. Rift Valley fever virus	+	++	+	++	+	+++	+	+	-	+	13
4. Sin Nombre virus	-	+++	+	+	+	++	+	+	+	+	12
2. EEE virus	+	+++	+	++	+	+	+	+	-	+	12
6. Junin virus	-	+++	+	++	+	+++	-	+	+	-	12
11.Tick-borne encephalits virus	+	+++	+	++	+	+	+	+	-	+	12
13.VEE virus	+	+++	+	++	+	+	+	+	-	+	12
14.WEE virus	+	+++	+	++	+	+	+	+	-	+	12
15.Yellow fever virus	+	++	+	++	+	++	-	+	-	+	11
5. Hantaan virus	-	++	+	+	++	+	-	+	+	-	9
17.Nipah virus	-	++	+	+	-	++	-	+	+	-	*8*
18. Chikun-Gunya fever virus	-	++	+	+	-	+	-	+	+	+	8
19. Dengua fever virus	-	++	+	+	-	+	-	+	+	+	8
20. Omsk fever virus	-	++	+	+	-	+	-	+	+	+	8

Table 3. Animal pathogens assessment according to criteria for selecting pathogens as biological warfare agents.

Animal pathogens	Weapo-nized	Severe socio-economic/ human health impacts	High morbidity/ mortality rates	Short incu-bation period	High transmiss-ibility/ contagi-ousness	Low infective or toxic dose	Difficult to diagnose/ identify at an early stage	Stability in the environ-ment	Lack of availability of cost effective protection/ treatment	Ease of produ-ction	Totals +/-
1. African swine fever virus	+	+	+	+	+	+	+	+	+	+	10/0
2. Avian influenza virus (Fowl plague virus)	+	+	+	+	+	+	+	+	+	+	10/0
3. Rinderpest virus	+	+	+	+	+	+	+	+	-	+	10/0
4. Bacillus anthracis	+	+	+	+	+	+	+	+	+	+	10/0
5. Classical swine fever virus (Hog cholera v.)	+	+	+	+	+	+	+	+	-	+	9/1
6. Foot and mouth virus	+	+	+	+	+	+	+	+	-	+	9/1
7. Pest des petits ruminants virus	+	-	+	+	+	+	+	+	+	+	9/1
8. Newcastle disease virus	+	+	+	+	+	+	+	+	-	+	9/1
9.Teschen disease virus (Porcine enterovirus type 1)	-	+	+	+	+	+	+	+	+	+	9/1
10. Vesicular stomatitis virus	-	+	+	+	+	+	+	+	+	+	9/1
11. Bulkholderia (Pseudomonas) mallei	+	+	+	+	-	+	+	+	+	+	9/1
12. Bluetongue virus	-	+	+	+	-	+	+	+	+	+	8/2
13. African horse sickness virus	-	+	+	+	+	+	+	+	+	-	8/2
14. Rift Valley fever virus	-	+	+	+	+	+	+	+	+	-	8/2
15. Brucella spp.	+	+	-	-	+	+	+	+	+	+	8/2
16. Contagious bovine (pleuropneum.) (M. mycoides var. mycoides type SC) (CBPP)	-	+	+	-	+	+	+	+	+	+	8/2
17. Nipah swine encephalitis virus	-	+	+	+	-	+	+	+	+	-	7/3
18. Camel pox virus	-	-	+	+	-	+	+	+	+	-	5/5
19.Contagious caprine (pleuropneum.) (M. capri-culum var. capri pneumoniae type F38) (CCPP)	-	-	-	-	+	+	+	+	+	+	5/5
20. Lumpy skin disease virus	-	-	-	+	-	+	+	+	+	-	4/6

Table 4. Animal pathogens assessment according to criteria for selecting pathogens as terrorism agents.

Animal pathogens	Severe socio-economic/ human health impacts	High morbidity/ mortality rates	Short incu-bation period	High contagiousness/ transmiss-ibility by contact, respiratory route, or both	Low infective/ toxic dose	Difficult to diagnose/ identify at an early stage	Stability in the environ-ment	Low effective or cost-effective prophylaxis/ protection/ treatment	Ease of produ -ction	Total (13)
1. African swine fever virus	+	+++	+	+++	+	+	+	+	+	13
2. Avian influenza virus (Fowl plague virus)	+	+++	+	+++	+	+	+	+	+	13
3. Vesicular stomatitis virus	+	+++	+	+++	+	+	+	+	+	13
4. Foot and mouth virus	+	+++	+	+++	+	+	+	-	+	12
5. Rinderpest virus	+	+++	+	+++	+	+	+	-	+	12
6. Newcastle disease virus	+	+++	+	+++	+	+	+	-	+	12
7. Classical swine fever virus (Hog cholera v.)	+	+++	+	+++	+	+	+	+	-	12
8. Bacillus anthracis	+	+++	+	+++	+	-	+	-	+	11
9. Contagious bovine (pleuropneum.) (M. mycoides var. mycoides type SC) (CBPP)	+	++	-	+++	+	+	+	-	+	10
10. Bluetongue virus	+	+	+	+++	+	+	+	-	+	10
11.Rift Valley fever virus	+	+++	+	+	+	+	+	-	+	10
12. Pest des petits ruminants virus	+	+++	+	+	+	+	+	-	+	10
13. Bulkholderia (Pseudomonas) mallei	+	+++	+	-	+	+	+	+	+	10
14. Nipah swine encephalitis virus	+	++	+	+	+	+	+	+	-	9
15. Teschen disease virus (Porcine enterovirus type 1)	-	+	+	+	+	+	+	+	+	8
16. African horse sickness virus	-	+++	+	+	+	+	-	+	-	8
17. Camel pox virus	-	++	+	+	+	+	+	+	-	8
18. Brucella spp.	+	+	-	++	+	-	+	-	+	7
19. Lumpy skin disease virus	-	+	+	+	+	+	+	+	-	7
20. Contagious caprine (pleuropneum.) (M. capri-culum var. capri pneumoniae type F38) (CCPP)	-	++	-	+	+	+	+	-	+	7